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Heart Rate Variability (HRV) is Extubation Failure Predictor in Pediatrics?

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Abstract

Background: Heart rate variability (HRV) is an indicator of autonomic activity in the regulation of circulation and changes have been associated with several pathological conditions.

Aims: The aim of the study was to acess the HRV as a predictor of extubation failure in pediatrics.

Methods: In this prospective observational pilot study, we included all consecutive patients from 1 month to 18 years of age who were admitted to the PICU in the ICr-HCFMUSP, São Paulo - Brazil. They were submitted to the spontaneous breathing test (SBT) and evaluated by HRV by the time and frequency domain variables derived from the Polar V800 equipment and the Kubios HRV Standart® program.

Results: A total of 36 patients [age 17 (2-216) months; male/female: 20/16; PIM2 3.9 (0.3-45.5); CRP (C-reactive protein) 20.2 (0.1-327); time of mechanical ventilation 5.0 (1.0-64.0) days] were included the study. The main diagnoses were 17 patients with lung diseases, 06 liver diseases, 08 neurological diseases, 03 sepsis/ septic shock, 01 nephropatic and 01 gastric disease. The data analyzed on HRV described in Table 3.

Conclusions: From the data analyzed, it can be concluded that the analysis of heart rate variability was not a predictor of success/failure of tracheal extubation for the pediatric sample studied.

Introduction

Breathing is one of the fundamental foundations of human life, necessaryfor survival and related to the intrinsic mechanism of the respiratory system. Ventilatory insufficiency is the inability to maintain the effective exchange of oxygen (O_2) and carbon dioxide (CO_2).[1] Mechanical ventilation (MV) is a frequent procedure for ventilatory support in patients with acute ventilatory insufficiency (IVA). It is invasive, expensive, and linked to potential risks (pneumonia, pulmonary injury associated with MV, hemodynamic changes, decreased respiratory muscle strength and endurance, and prolonged ICU stay).[1-4] Ventilatory weaning in pediatric patients is desirable and should be started 24 hours after orotrache-

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al intubation (OTI).[5-7] The process of withdrawal from ventilatory support occupies about 40-50% of the total time of MV.[8,9] Weaning protocols reduce MV time and ICU stay.[2,10,11] The pathophysiology of ventilatory weaning failure is complex and involves the interaction betweencardiorespiratory reserve, autonomic functioning and the musculoskeletal capacity of the individual.[6,12] ICU patients generally present metabolic,endocrine, neurological, muscular and immunological alterations, which may alter the weaning time of MV.[1,5,12] Early use of spontaneous ventilatory modes such as synchronized intermittent MV (SIMV) and supportive pressure ventilation (SPV) facilitates the weaning process of MV and tracheal extubation. These modes are well tolerated by most pediatric patients and allow shorter MV time and earlier extubation.[13,14]

The spontaneous breathing test (SBT) is considered one of the successful predictors of weaning and extubation.[6] In the ICU, SBT is a common practice because it allows the assessment of children's cardiorespiratory tolerance during minimum ventilatory support.[8,9] The sensitivity of SBT is 83%to recognize children who have a chance of successfully withdrawing ventilatory support. Thus, there is a higher proportion of successful extubations than failures.[8] The reintubation rate is related to the increased morbidity and mortality of ICU patients.[15] Methods of cardiorespiratory behavior analysis have been applied inclinical studies of ventilatory weaning and tracheal extubation, which demonstrate that healthy biological systems have innate and highly complex patterns of cardiorespiratory variability. However, when these systems present conditions, the variability is altered and the complexity reduced. This decreaseis indicative of reduced adaptability, reflects changes in cardiorespiratory systems and has been described as a marker of results in several clinicalsituations. Cardiorespiratory variation is related to the balance of the sympathetic and parasympathetic systems of the thermal, respiratory and cardiac control functions.[11,16-19]

The assessment of heart rate variability (HRV) has been a predictor of success in ventilatory weaning in adult patients.[5,11,19,20] The combination ofcardiorespiratory variation and clinical response to SBT had better accuracy of tracheal extubation success than any other predictor evaluated alone.[14] A similar result was observed when applying cardiorespiratory variability in the neonatal population.[19,21] However, there are not published studies on HRV in the pediatric population related to ventilatory weaning and tracheal extubation. Therefore, theaim of this study was to verify the applicability of HRV as a predictor of failure / success of tracheal extubation in the pediatric population.

Method

This prospective cross-sectional clinical trial, including a conveniencesample of patients admitted to the PICU of FMUSP, from November 2017 to July 2018. We evaluated children of both genders, aged between 30 days and 17 years, 11 months and 29 days of life. Study approved by the Institution (CEP nº 13.267/2015). Children undergoing MV for more than 24 hours and with clinical eligibility criteria for SBT[22] were included; those with tracheostomy, with orotracheal tube escape (with or without cuff) ≥15% were excluded.

HRV analysis was applied throughout the SBT, which consisted of keeping the child breathing spontaneously, in the supportive pressure ventilation (PSV) modality for 60 minutes (according to the PICU pre-existing protocol). The ventilatory parameters used in this ventilatory modality were: support pressure (SP): 10-7cm H_20; positive end-expiratory pressure (PEEP): 5-6cm H_20; inspired fraction of O_2(FiO_2): the lowest possible for O_2 saturation values (SpO_2) ≥ 90%, provided it was ≤50%. The variables analyzed during the SBT were: HRV variables - time domain (mean RR, mean HR, RMSSD, pNN50) and frequency domain (LF, HF, LF / HF ratio). These data were collected at eight different times during the SBT: five minutes before the test; five, 15, 30, 45 and 60 minutes of test; five and 30 minutes after the end of the test. After recording these variables in the data collection form, the child was or was not elected for tracheal extubation; considering only the success criteria of SBT (maintenance of respiratory rate, cardiac rate and SpO_2 stability; maintenance of minute volume during SBT; absence of use of accessory respiratory muscles during the test);[22] HRV analysis data were not used to determine whether or not the child would be extubated. Statistical analysis of HRV variables was performed only after the completion of the weaning / extubation process of each patient.

Criteria for discontinuation of the study protocol were: variation of vital signs (HR, RF and BP) above or below 30% of predicted for age; SpO_2 lower than 88% or need to increase FiO_2 during test. The presence or absences of signs of respiratory distress were also considered, such as the use of accessoryrespiratory muscles, pallor, sweating and/or psychomotor agitation. In the presence of any changes mentioned above, the SBT was interrupted and the child returned to ventilatory mode prior to the test. After 24 hours of respiratory muscle rest, the child could perform a new SBT.[22] To measure vital signs during SBT, the Dixtal® multiparametric monitors (DX 2010; DX 2023; 2022), present in each PICU bed, were used. For HRV data, Polar® V800 was used and their conversion using the Kubios HRV Standard® program. MV was performed using the following devices: E500 (Newport Medical Instruments®) and Servo I (Maquet Medical Instruments®).

The tests were performed by trained physical therapists. Data were entered into the SPSS 17.0 program and double-checked for consistency. For statistical analysis, the Kolmogorov-Smirnov (KS) test was used to adhere tothe Gauss curve and to pair the sample. For the parametric variables, Student's t-test was used and the results presented as mean and standard deviation; nonparametric variables were analyzed using Fisher's chi-square test and presented as median (minimum-maximum) or median and interquartile ranges 25%-75%; variables with three or more measurements were analyzed by the one-way ANOVA test. HRV parameters were described according to extubation success using summary measures and verified the influence of theseparameters on extubation success using generalized estimation equations (EEG) with binomial distribution and log it binding function, assuming an autoregressive correlation matrix of first order between attempts[23]. Microsoft Excel 2003 software was used for data tabulation and statistical analyzes were performed using IBM-SPSS® for Windows version 22.0 software; considering statistically significant when p≤0.05. Results are presented in tables.

Results

In 2017 there were 571 hospitalizations in the PICU where data were collected for this research, and 221 (38.7%) patients received invasive ventilatory support with extubation failure of 10.8% (N = 24 children); in 2018 there were 565 hospitalizations with 205 (33.6%) patients undergoing invasive ventilatory support with extubation failure of 12.7% (N = 26 children). During thisstudy (from November 2017 to July 2018) approximately 420 children were admitted to the PICU, of which 147 (35%) used invasive ventilatory support and 55 patients were considered eligible for SBT, and 36 patients met the criteria of inclusion for this study. During this study period, extubation failure occurred in 11% (N = 16 children) of the total sample of 147 children undergoing invasive ventilatory support. During the study period, 55 patients were eligible for SBT. Of these, 19 were excluded due to the following reasons: 12 due to non-signature of the consent form due to the absence of the presence of legal guardians before data collection for this research; five (05) due to interference with the Polar® monitor signal during SBT; two (02) due to having performed T-tube SBT. In the study, included 36 patients, 43 SBT were performed, since five patients required more than one SBT during PICU admission to present clinical conditions for extubation. The epidemiological data of the total study sample are presented in Table 1, just as the variables of MV are in Table 2. Failure and successful extubation groups were compared for HRV parameters (Table 3), in which it was observed that there was no statistically significant difference between them. By identifying the most frequent subgroupin this study by clinical diagnosis, it was observed that 47.2% of the sample cosnsisted of patients with a primary diagnosis of respiratory cause (Table 1), whose demographic and ventilatory characteristics are presented in Tables 4 and 5. When comparing the extubation success versus failure groups specifically for this subgroup, it was also observed that there was no statistically significant difference for HRV variables (Table 6).

Table 1: Description of the demographic characteristics of the evaluated patients.

Variable	Description (N=36)
Age (months)	
mean ± SD	49,7 ± 61,3
median (min; max.)	17 (2; 216)
Weight (Kg)	**(N = 32)**
mean ± SD	14,9 ± 13,1
median (min; max.)	10 (3; 58)
PIM 2	**(N = 27)**
mean ± SD	8,8 ± 12,8
median (min; max.)	3,9 (0,3; 45,5)
CRP admission	
mean ± SD	50,2 ± 79,7
median (min; max.)	20,2 (0,1; 327)
Gender, n (%)	
Feminine	16 (44,4)
Male	20 (55,6)
Primary diagnosis, n (%)	
Pneumo	17 (47,2)
Hepato	6 (16,7)
Neuro	8 (22,2)
Sepsis / Septic Shock	3 (8,3)
Nephro	1 (2,8)
Gastro	1 (2,8)
Secondary diagnosis, n (%)	**(N = 18)**
Neuro	8 (44,4)
Sepsis / Septic Shock	5 (27,8)
Onco / Hemato	2 (11,1)
Cardio	1 (5,6)
Nephro	1 (5,6)
Hepato	1 (5,6)

Caption: SD = Standard Deviation; Kg = pounds; PIM2 = Pediatric Index of Mortality; CRP = C-Reactive Protein

Table 2: MV variables during SBT.

Variable	Description (N=43)
VPM Time (days)	
mean ± SD	8,3 ± 10,7
median (min; max.)	5 (1; 64)
PS	
mean ± SD	15,9 ± 2,5
median (min; max.)	16 (8; 20)

PEEP	
mean ± SD	6,58 ± 0,76
median (min; max.)	6 (5; 9)
FiO2	
mean ± SD	0,32 ± 0,07
median (min; max.)	0,3 (0,21; 0,45)
PNM assoc MV, n (%)	
Not	41 (95,3)
Yes	2 (4,7)
Sedation, n (%)	
Not	13 (30,2)
Yes	30 (69,8)

Caption: MV = mechanical ventilation; SD = standard deviation; PS = support pressure; PEEP = positive end-expiratory pressure; FiO2 = inspired oxygen fraction; PNM = pneumonia; Assoc = Associated

Table 3: Description of HRV parameters according to extubation failure/success and comparative test results.

Variable	Extubation Success		Total (N = 43)	p
	Not (N = 16)	Yes (N = 27)		
Mean RR			0,656	
mean ± SD	579 ± 257,9	551,7 ± 196,1	561,9 ± 218,5	
median (min; max.)	473,4 (380,1; 1409,4)	472,7 (392,4; 1119)	472,7 (380,1; 1409,4)	
STD RR			0,744	
mean ± SD	5030,4 ± 16641,9	3615,7 ± 12303,5	4142,1 ± 13896	
median (min; max.)	483,1 (2,4; 67282,7)	530 (4,7; 64158,6)	530 (2,4; 67282,7)	
Mean HR			0,717	
mean ± SD	115,5 ± 30,7	118,4 ± 29,5	117,3 ± 29,6	
median (min; max.)	127 (42,6; 157,8)	126,9 (53,6; 152,9)	126,9 (42,6; 157,8)	
RMSSD			0,964	
mean ± SD	1443,7 ± 4076,7	1499,8 ± 4650,2	1478,9 ± 4395,8	
median (min; max.)	411,7 (1,8; 16624,4)	263,2 (3,8; 24230,9)	335,1 (1,8; 24230,9)	
pNN			0,906	
mean ± SD	24,5 ± 29,2	23,6 ± 28	24 ± 28,1	
median (min; max.)	11,6 (0; 95,7)	14,4 (0; 92,3)	14,2 (0; 95,7)	
LF			0,950	
mean ± SD	0,06 ± 0,03	0,06 ± 0,02	0,06 ± 0,02	
median (min; max.)	0,05 (0,04; 0,14)	0,05 (0,04; 0,11)	0,05 (0,04; 0,14)	
HF			0,376	
mean ± SD	0,2 ± 0,05	0,19 ± 0,07	0,19 ± 0,06	
median (min; max.)	0,18 (0,15; 0,29)	0,16 (0,15; 0,4)	0,17 (0,15; 0,4)	
LF / HF			0,820	
mean ± SD	13,2 ± 23,5	11,9 ± 15,7	12,4 ± 18,7	
median (min; max.)	4,6 (0,4; 91,5)	4,5 (0,5; 53,9)	4,5 (0,4; 91,5)	

Caption: Mean R-R = mean interval R-R; Mean HR = mean heart rate; RMSSD = square root of sum of successive differences between normal R-R intervals adjacent to square; pNN = percentage of normal R-R intervals; LF = low frequency; HF = high frequency; LF / HF = low frequency / high frequency ratio; GEE = generalized equivalent equations

Table 4: Description of demographic characteristics of patients with the main diagnosis "respiratory disease".

Variable	Description (N=17)
Age (months)	
mean ± SD	29,1 ± 41,2
median (min; max.)	11 (2; 132)
Weight (Kg)	**(N = 16)**
mean ± SD	9,3 ± 5,4
median (min; max.)	7,9 (4; 22)
PIM 2	**(N = 12)**
mean ± SD	7,8 ± 9,8
median (min; max.)	2,5 (0,4; 28,1)
CRP admission	
mean ± SD	55,1 ± 86,3
median (min; max.)	25,7 (0,3; 279,6)
Gender, n (%)	
Feminine	7 (41,2)
Male	10 (58,8)
Secondary diagnosis, n (%)	**(N = 18)**
Cardio	1 (9,1)
Hepato	1 (9,1)
Neuro	5 (45,5)
Sepsis/ Septic Shock	4 (36,4)

Caption: SD = standard deviation; Kg = pounds; PIM 2 = Pediatric Index of Mortality; CRP = C-reactive protein

Table 5: MV variables during SBT.

Variable	Description (N=22)
VPM Time (days)	
mean ± SD	7,5 ± 6,9
median (min; max.)	4,5 (1; 27)
PS	
mean ± SD	16,4 ± 2,5
median (min; max.)	16,5 (8; 20)
PEEP	
mean ± SD	6,73 ± 0,83
median (min; max.)	7 (6; 9)
FiO2	

mean ± SD	0,33 ± 0,07
median (min; max.)	0,35 (0,21; 0,45)
PNM assoc MV, n (%)	
Not	20 (90,9)
Yes	2 (9,1)
Sedation, n (%)	
Not	9 (40,9)
Yes	13 (59,1)

Caption: MV = mechanical ventilation; SD = standard deviation; PS = support pressure; PEEP = positive end-expiratory pressure; FiO2 = inspired oxygen fraction; PNM = pneumonia; Assoc = Associated

Table 6: Description of HRV parameters comparing extubation failure/ success groups of patients diagnosed with "respiratory disease".

Variable	Extubation Success		Total (N = 43)	p
	Not (N = 16)	Yes (N = 27)		
Mean RR				0,325
mean ± SD	601,3 ± 342,4	487,3 ± 135,6	533,9 ± 241,8	
median (min; max.)	447,6 (380,1; 1409,4)	435,6 (398,2; 904,9)	446,2 (380,1; 1409,4)	
STD RR				0,458
mean ± SD	8436,2 ± 22117,1	1158,8 ± 2230,3	4135,9 ± 14233,9	
median (min; max.)	100,1 (2,4; 67282,7)	40 (4,7; 7798,7)	84,9 (2,4; 67282,7)	
Mean HR				0,465
mean ± SD	118,4 ± 38,1	129 ± 23,4	124,6 ± 29,9	
median (min; max.)	134,1 (42,6; 157,8)	137,7 (66,3; 150,7)	134,5 (42,6; 157,8)	
RMSSD				0,425
mean ± SD	2233 ± 5429	436,9 ± 679,6	1171,7 ± 3508,4	
median (min; max.)	117,8 (1,8; 16624,4)	49,9 (3,8; 2134,3)	99,6 (1,8; 16624,4)	
pNN				0,261
mean ± SD	30,6 ± 35,9	15,4 ± 25,4	21,6 ± 30,3	
median (min; max.)	13,1 (0; 95,7)	2,3 (0; 88,3)	6,7 (0; 95,7)	
LF				0,943
mean ± SD	0,06 ± 0,03	0,06 ± 0,02	0,06 ± 0,02	
median (min; max.)	0,05 (0,04; 0,14)	0,05 (0,04; 0,11)	0,05 (0,04; 0,14)	
HF				0,886
mean ± SD	0,2 ± 0,06	0,19 ± 0,07	0,2 ± 0,07	
median (min; max.)	0,16 (0,15; 0,29)	0,16 (0,15; 0,39)	0,16 (0,15; 0,39)	
LF / HF				0,427
mean ± SD	19,7 ± 29,9	12,3 ± 15,7	15,3 ± 22,3	
median (min; max.)	7,4 (0,4; 91,5)	6,2 (1; 53,9)	6,8 (0,4; 91,5)	

Caption: Mean R-R = mean R-R interval; Mean HR = mean heart rate; RMSSD = square root of sum of successive differences between normal R-R intervals adjacent to square; pNN = percentage of normal R-R intervals; LF = low frequency / HF = high frequency; LF / HF = low frequency / high frequency ratio; GEE = generalized equivalent equations

Discussion

The present study aimed to verify whether HRV is a predictor of success/failure of tracheal extubation in pediatrics. The main results were that HRV was not a predictor of success/failure of tracheal extubation in this sample,not even when the analysis occurred in the subgroup "respiratory disease" (higher number of hospitalized patients in the analyzed period - 47.2%). It is possible to determine a cutoff point for HRV variables for this group of patients. Determining the optimal time to start ventilatory weaning remains a majorchallenge in PICU. Long term MV stay is associated with important complications such as pneumonia and changes in muscle strength and endurance, increased morbidity and mortality. However, it is known that early weaning can be harmful to patients, especially in the pediatric population.[24] Ventilatory weaning/tracheal extubation protocols aim to reduce MV time and ICU stay.[6,25,26] A standardized approach to managing the management of the ventilatory weaning process contributes to reducing MV time and improving clinical outcomes for the patient.[24,27] For the discontinuation of ventilatory support, decision-making is expected to be based on tests, criteria and objectives that determine the appropriate time for its initiation and completion with the success of tracheal extubation.[24,28] The most frequently used strategy for ventilatory weaning of infants and children is clinical judgment and the gradual reduction of ventilatory parameters. Extubation is usually performed based on minimum ventilatory support parameters or after SBT.[29]

Several studies[30-34] discuss the optimal duration of SBT, and some have previously shown that SBT lasting between 30 minutes and two hours was sufficient to consider patients fit or not for tracheal extubation. In our study, the SBT time was 60 minutes and was performed in PSV ventilatory mode, according to institutional protocol. Cardiovascular changes can be assessed in several ways, including HRV analysis. The study of HRV is a noninvasive and selective method that evaluates autonomic modulation.[35,36] This analysis demonstrates the interaction of the sympathetic and parasympathetic autonomic system in the face of different clinical situations, such as the presence of respiratory and/orneurological diseases and/or routine ICU procedures, such as respiratory physiotherapy and ventilatory weaning.[35,36] Marsilio L et al, 2019[37] conducted an observational study with 17 childrenin a university hospital (age 1.21 [0.28; 14.81] years) and evaluated their HRVin the first 24 hours of stay in the PICU and in the last 24 hours after the resolution of the underlying disease. As in our study, the time domain variables were evaluated: RMSSD, pNN50 and SDNN and from the collected data, concluded that HRV is a marker of recovery in severely ill children, considering that HRV significance was observed at to compare the data of the first with the last 24 hours of the child's stay in PICU.[37] The instability of the autonomic system occurs before the deterioration of clinical signs or the results of laboratory tests in newborns (NB),[38] which also seems to occur in the pediatric age group.[37]

The study by Kaczmarek J *et al* 2013[38] compared HRV differences between NB (N = 47 NB; weight ≤ 1,250 grams) successfully versus tracheal extubation failure, as well as assessing HRV accuracy as a predictor of tracheal extubation readiness. They concluded that infants who failed the first attempt at tracheal extubation had a reduced HRV during SBT.[38] Neural mechanisms are responsible for regulating inflammation, so the literature suggests an association between HRV and inflammation/infection.[39,40] Respiratory infections, such as pneumonia and bronchiolitis, which are commonin children, trigger an inflammatory process with release of specific inflammatory mediators (bronchiolitis → IL8; pneumonia → C-reactive protein - CRP).[39,40] Marsland AL *et al*[41] demonstrated that decreased vagal activity is associated with increased inflammation, as Sloam *et al*[40] found results confirming the hypothesis that lower vagal activation is related to increased proinflammatory cytokine production. These are present in many different inflammatory processes, such as respiratory diseases, however, this information has not been studied in the pediatric population. Based on this information, the prospective study by Jacinto CP[42] aimed to assess changes in HRV resulting from impaired cardiac autonomic performance in infants diagnosed with acute viral bronchiolitis (AVB).We included 24 children (mean age 6±2 months) subdivided into two groups (control: no respiratory disease; intervention: with AVB). From the results obtained, they concluded that respiratory physiotherapy and nasotracheal aspiration, both used for airway clearance, promote improvement in HRV autonomic modulation in infants diagnosed with AVB.[42]

In our study, HRV was not a predictor of tracheal extubation failure/success, even when the subgroup “respiratory disease” was analyzed. This result is believed to be due to the heterogeneous pediatric population studied (mean age 49.7±61.3; mean weight 14.9±13.1; CRP admission 50.2±79.7). The maturation of the sympathetic and parasympathetic systems is known to accompany the child's growth. Therefore, there is a growing increasein autonomic modulation in the pre and postnatal periods.[42] This factor mayhave contributed to the fact that HRV was not statistically significant as apredictor of tracheal extubation failure/success. The absence of previous studies in pediatrics with subgroup analysis for specific diseases / pathophysics make it difficult to compare behavior in the process of ventilatory weaning/tracheal extubation in this age group.[36,42] In general, the studies are based on short-term HRV records and involve heterogeneous groups with divergent results.[36,42]

Thus, our study was unable to detect HRV influences as a determinant ofextubation success/failure in the sample studied, specifically in those diagnosedwith respiratory disease. However, some limitations of the study may haveinterfered with the results, such as: age heterogeneity and small sample size (although previous studies included around 20 children). The continuity of this study is necessary to confirm the findings from the analysis of 43 SBT.

Conclusion

From the data analyzed, it can be concluded that the analysis of heartrate variability was not a predictor of success/failure of tracheal extubation for the pediatric sample studied. The continuity of the study is suggested to confirm the findings.

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None.

Conflict of Interest

The author declared no conflicts of interest.

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